An updated review on morpholine derivatives with their pharmacological actions

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Abstract—The invention of newer chemical entities, which have some therapeutically worth is always a great challenge. It is no doubt that it is a lengthier process. We have several drugs in the market for treatment of wide variety of diseases. The marketed drugs available may be heterocyclic or non-heterocyclic derivatives. Always it was found that heterocyclic derivatives have wide variety of pharmacological activity. The intension of this review is to highlight one of the important heterocyclic rings i.e.: Morpholine. Several works have been done on this nucleus, which should be enlighten for more and more applicability.

Keywords—heterocyclic compound, morpholine, disease, therapeutic agents.
Introduction

Morpholine is physically a liquid with no color. It has fish-like or ammonia odor. It is mostly used as a solvent, brightener for detergents, corrosion inhibitor, rubber accelerator & boiler water additive. It found to be a base because when it is treated with HCl it produces morpholinium chloride salt. Morpholinium is its conjugate acid.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
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<tbody>
<tr>
<td>General properties of morpholine</td>
</tr>
<tr>
<td><strong>MORPHOLINE</strong></td>
</tr>
<tr>
<td>Mol. Formula = C₄H₉NO</td>
</tr>
<tr>
<td>Mol. Weight = 87.12036</td>
</tr>
<tr>
<td>Composition = N (16.08%), H (10.41%), O (18.36%), C (55.15%)</td>
</tr>
<tr>
<td>Molar Refractivity = 23.40 ± 0.3 cm³</td>
</tr>
<tr>
<td>Molar Volume = 93.5 ± 3.0 cm³</td>
</tr>
<tr>
<td>Index of Refraction = 1.414 ± 0.02</td>
</tr>
<tr>
<td>Parachor = 217.6 ± 4.0 cm³</td>
</tr>
<tr>
<td>Surface Tension = 29.2 ± 3.0 dyne/cm</td>
</tr>
<tr>
<td>Monoisotopic Mass = 87.068414 Da</td>
</tr>
<tr>
<td>Density = 0.931 ± 0.06 g/cm³</td>
</tr>
<tr>
<td>Average Mass = 87.1204 Da</td>
</tr>
<tr>
<td>Polarizability = 9.27 ± 0.5 10⁻²⁴cm³</td>
</tr>
<tr>
<td>Nominal Mass = 87 Da</td>
</tr>
</tbody>
</table>

Morpholine is a 6-membered heterocyclic compound where we can find two hetero atoms, Oxygen & Nitrogen. The medicinal compound which contains this basic nucleus possess wide variety of pharmacological activity. Several medicinal compounds which have morpholine nucleus are available in the market and in existing condition too. Some important drugs with their uses are listed below.

Morpholine derivatives & uses

Afobazole

5-ethoxy-2-[2-(morpholino)-ethylthio]-benzimidazole
**Mechanism of action:** [1^-3]

**Afobazole**

- GABAergic
- NGF and BDNF-release-promoting
- MT1 receptor agonism
- MT3 receptor antagonism
- Sigma agonism

**Fig 1. Mechanism of action of Afobazole**

*Uses:* It is used as an *Anxiolytic* drug. [4]

**Aprepitant**

![Aprepitant](image)

5-[(2R,3S)-2-(I-1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy)-3-(4-fluorophenyl)morpholino]methyl]-1H-1,2,4-triazol-3(2H)-one

**Mechanism of action:** [5]

**Fig 2. Mechanism of action of Substance-P**

**Uses:** Substance-P antagonists [6]
**Bazinaprine**

![Chemical structure of Bazinaprine](image)

3-[[2-\{morphpolin-4-yl\}ethyl]amino]-6-phenylpyridazine-4-carbonitrile

**Mechanism of action:** Bazinaprine is act by inhibiting enzyme, **monoamine oxidase**. [7]

**Uses:** Useful for the treatment of depression[7]

**Canertinib**

![Chemical structure of Canertinib](image)

N-\{4-\{3-Chloro-4-fluorophenyl\}amino\}-7-\{3-\{morphpolin-4-yl\}propoxy\}quinazolin-6-yl\}prop-2-enamide

**Mechanism of action:** It is an **irreversible tyrosine-kinase inhibitor** with activity against HER-2 (IC\_50 19 nM), EGFR (IC\_50 0.8 nM) and ErbB-4 (IC\_50 7 nM).[8]

**Uses:** Experimental drug candidate for the treatment of cancer.[8]

**Cobicistat**

![Chemical structure of Cobicistat](image)

Thiazol-5-ylmethyl N-[1-benzyl-4-[[2-\{2-isopropylthiazol-4-yl\}-methyl-methylcarbamoyl]amino]-4-morpholino-butanoyl]amino]-5-phenyl-pentyl]carbamate

**Mechanism of action:** Cobicistat is act by inhibiting CYP3A which is helpful to increase systemic exposure of Darunavir & Atazanavir in combination with other antiretroviral.

**Uses:** Used in the treatment of infection with the **human immunodeficiency virus (HIV)**.[10]
**Dextromoramide**

![Dextromoramide structure](image)

(3R)-3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-yl-butan-1-one

**Mechanism of action:**

It acts as an Opioid analgesic.\[^{11}\]

**Uses:** It is used for cancer pain relief.\[^{12}\]

**Doxapram**

![Doxapram structure](image)

1-ethyl-4-(2-morpholin-4-ylethyl)-3,3-diphenyl-pyrrolidin-2-one

**Mechanism of action:**\[^{13}\]

(Fig 3. Mechanism of action of Doxapram)

**Uses:** It is used as a respiratory stimulant.\[^{14}\]
Edivoxetine

(1R)-2-(5-fluoro-2-methoxyphenyl)-1-[(2S)-morpholin-2-yl]-1-(tetrahydro-2H-pyran-4-yl)-ethanol

Mechanism of action:
It acts as a selective norepinephrine reuptake inhibitor. ([15]
Uses: It is in phase III clinical trials for major depressive disorder. ([16]

Emodepside
**Mechanism of action:** [17]

![Fig 4. Mechanism of action of Emodepside](image)

**Uses:** It is used as Anthelmintic drug [18]

**Esreboxetine**

![Chemical structure of Esreboxetine](image)

(2S)-2-[(S)-(2-ethoxyphenoxy)-phenyl-methyl]-morpholine

**Mechanism of action:**
It acts by inhibition of Selective norepinephrine reuptake [19]

**Uses:** It was under development for the treatment of neuropathic pain and fibromyalgia [19].
**Fenbutrazate**

![Fenbutrazate structure](image)

2-(3-methyl-2-phenylmorpholin-4-yl)ethyl 2-phenylbutanoate

**Mechanism of action:**
It is act as a psychostimulant

**Uses:** Used as an appetite suppressant. [20]

**Filendalodol**

![Filendalodol structure](image)

(1R,2S)-1-(1,3-benzodioxol-5-yl)-1-(4-morpholiny}-2-propanol

**Mechanism of action:**
It is effective on LTB4, bradykinin, PGE2, PAF or IL-1 beta-induced Hyperalgesia it causes decrease in pain threshold in the rat paw pressure model. [21]

**Uses:** Analgesic drug [22]

**Gefitinib**

![Gefitinib structure](image)

N-(3-chloro-4-fluoro-phenyl)-7-methoxy- 6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine
**Mechanism of action:**[23]

(Fig 5. Mechanism of action of Gefitinib)

Uses:
Used for certain breast, lung and other cancers [24]

**Indeloxazine**

\[
2-(3\text{H}-\text{inden-4-yloxymethyl})\text{-morpholine}
\]
Mechanism of action: [25-27]

Fig 6. Mechanism of action of Indeloxazine

Uses:
Treatment of cerebrovascular disease[^28]

**Landiolol**

![Landiolol structure]

\[(4S)-2,2\text{-dimethyl}-1,3\text{-dioxolan}-4\text{-yl}]\text{-methyl}\text{-}3\text{-[4-[(2S)-2\text{-hydroxy}-3\text{-[2\text{-morpholine}-4\text{-carbonylamino\text{-ethyloxy\text{-propoxy\text{-phenyl\text{-propanoate}}}}}

Mechanism of action:
It is an ultra-short-acting β1-selective blocking agent. It is thought to reduce the sympathetic drive, resulting in reduction in heart rate, decrease in spontaneous firing of ectopic pacemakers, slowing the conduction and increase the refractory period of the AV node. [^29]

Uses: Anti-arrhythmic drug [^30]

**Linezolid**

![Linezolid structure]

\((S)-N\text{-}[3\text{-[3\text{-fluoro}-4\text{-[morpholin\text{-4\text{-yl\text{-phenyl\text{-2\text{-oxo\text{-1\text{-oxazolidin\text{-5\text{-yl\text{-methyl\text{-aceto}}}}}}}}}}}}\text{amide}}

[^28]: Treatment of cerebrovascular disease
[^29]: Mechanism of action
[^30]: Anti-arrhythmic drug
**Mechanism of action:** \[^{[31]}\]

![Mechanism of action of Linezolid](image1)

**Fig 7.** Mechanism of action of Linezolid

**Uses:** It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.\[^{[32]}\]

**Linsidomine**

![Structure of Linsidomine](image2)

5-imino-3-morpholin-4-yl-5H-1,2,3-oxadiazol-3-i-um-2-ide

**Mechanism of action:** \[^{[33]}\]

![Mechanism of action of Molsidomine](image3)

**Fig 8.** Mechanism of action of Molsidomine
Uses: It is used as Vasodilator[^33]

**Minaprine**

![Minaprine structure](image1)

4-methyl-N-(2-morpholin-4-ylethyl)-6-phenylpyridazin-3-amine

**Mechanism of action:**[^34]
It acts as a reversible inhibitor of MAO-A for anti-depressant activity.

Uses: It is used as anti-depressant[^35]

**Moclobemide**

![Moclobemide structure](image2)

4-chloro-N-(2-morpholin-4-ylethyl)benzamide

**Mechanism of action:**[^36-37]

![Moclobemide mechanism](image3)

Fig 9. Mechanism of action of Moclobemide

Uses: Used to treat depression and social anxiety[^38]
Molindone

3-ethyl-2-methyl-5-(morpholin-4-ylmethyl)-1,5,6,7-tetrahydro-4H-indol-4-one

Mechanism of action:[39]

Fig 10. Mechanism of action of Molindone

Uses: It is used in the treatment of schizophrenia[40]

Molsidomine

1-Ethoxy-N-(3-morpholino-5-oxadiazol-3-iumyl)methanimidate
Mechanism of action: [41]

Molsidomine

Active metabolite linsidomine

Releases nitric oxide (NO)

Vasodilation

Fig 11. Mechanism of action of Molsidomine

Uses: It is used as vasodilating agent. [42]

Moracizine

Ethyl-[10-(3-morpholin-4-ylpropanoyl)-10H-phenothiazin-2-yl]-carbamate

Mechanism of action: [43]

Moracizine

Inhibit rapid inward sodium current across myocardial cell membranes

Shorten cardiac transmembrane action potential

Supressing rapid ectopic activity

Fig 12. Mechanism of action of Moracizine
Morniflumate

2-morpholin-4-yethyl-2-[[3-(trifluoromethyl)phenyl]-amino]-nicotinate

Mechanism of action: It inhibits 5-lipoxygenase and cyclooxygenase pathways, which lead to fever and inflammation.\[45\]
Uses: It is used as non-steroidal anti-inflammatory drug.\[46\]

Moroxydine

N-(Diaminomethylidene)-morpholine-4-carboximidamide

Mechanism of action: It acts by an influence on the virus host-cell system.
Uses: It is used as anti-viral drug.\[47\]

Oxaflozane

2-yl-2-[3-(trifluoromethyl)-phenyl]morpholine

Mechanism of action: It is a prodrug of flumexadol. It is act as an agonist of the serotonin 5-HT\textsubscript{1A} and 5-HT\textsubscript{2C} receptors and, to a much lesser extent, of the 5-HT\textsubscript{2A} receptor.\[48\]
Uses: It is used as antidepressant and anxiolytic drug.\[49\]
Phendimetrazine

3,4-dimethyl-2-phenylmorpholine

Mechanism of action:

Fig 13. Mechanism of action of Phendimetrazine

Uses: Appetite suppressant drug.

Pholcodine

7,8-didehydro- 4,5α-epoxy- 17-methyl- 3- [2- (morpholin- 4- yl) ethoxy] morphinan- 6α-ol

Mechanism of action:

Fig 14. Mechanism of action of Pholcodine
**Uses:** It is a opioid cough suppressant (antitussive)[53]

**Pravadoline**

![Chemical structure of Pravadoline](image)

(4-methoxyphenyl)-[2-methyl-1-(2-morpholin-4-ylethyl)indol-3-yl]methanone

Mechanism of action: [54]
It acts by inhibiting the synthesis of prostaglandins (PGs).

Uses: It used is an antinflammatory and analgesic drug[54]

**Pseudophenmetrazine**

![Chemical structure of Pseudophenmetrazine](image)

(±)-cis-3-methyl-2-phenylmorpholine

Mechanism of action: [55]
Pseudophenmetrazine is one of the analogue of phendimetrazine (cis-configured) & a stereoisomer of the drug phenmetrazine. It shows its action by inhibiting or interfering dopamine reuptake.

Uses: It is used as psychostimulant compound.[55]

**Quizartinib**

![Chemical structure of Quizartinib](image)

1-{5-(tert-Butyl) hexantrh-3-yl}-3-(4-{7-(2-morpholinoethoxy)-benzo[d]-imidazo[2,1-b]thiazol-2-yl}phenyl)urea
Mechanism of action: 

Quizartinib

It binds to FLT3 tyrosine kinase receptor isoform

Inhibition of cancer cell proliferation

Death of cancer cell

**Fig 15. Mechanism of action of Quizartinib**

Uses: Under development for the treatment of acute myeloid leukaemia\[^{57}\]

**Racemoramide**

\[
\text{3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-yl-butano-1-one}
\]

Mechanism of action: Opioid analgesic.
Uses: It is used as opioid analgesic\[^{58}\]

**Radafaxine**

\[
\text{(+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethylmorpholin-2-ol}
\]
Mechanism of action: It is a norepinephrine–dopamine reuptake inhibitor.[59] Uses: Investigated for treatment of restless leg syndrome.[59]

**Reboxetine**

![Reboxetine molecule](image)

(R*,R*)-2-[(2-ethoxyphenoxy)-phenyl-methyl]morpholine

Mechanism of action: It is a selective norepinephrine reuptake inhibitor (NRI) which have 20-fold selectivity for the norepinephrine transporter (NET) over the serotonin transporter (SERT).

Uses: It is used in the treatment of panic disorder, clinical depression, and ADD/ADHD.[61]

**Retosiban**

![Retosiban molecule](image)

(3R,6R)-6-[(2S)-butan-2-yl]-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(morpholin-4-yl)-2-oxoethyl]piperazine-2,5-dione

Mechanism of action: [62]

- It acts as a competitive oxytocin receptor antagonist
- It blocks the oxytocin-mediated contraction of the uterine smooth muscle
- It prevents preterm labour & premature birth

Fig 16. Mechanism of action of Retosiban
Uses: It is used for the treatment of **preterm labor[^63]**

**Reversine**

N'-cyclohexyl-N-(4-morpholinophenyl)-7H-purine-2,6-diamine

Mechanism of action: It shows its action by central inhibitory action on several kinases enzymes concerned in cytokinesis & cell cycle regulation.

Uses: Used for **stem cell dedifferentiation[^64]**

**Rivaroxaban**

(S)-5-chloro-N-[[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]henanthren-5-yl]methyl] thiophene-2-carboxamide

Mechanism of action: [^65]

![Fig 17. Mechanism of action of Rivaroxaban](image-url)
Uses: It is used as oral anticoagulant[65]

**Rocuronium bromide**

![Chemical structure of Rocuronium bromide]

\[\text{1(2S,3S,5S,8R,9S,10S,13S,14S,16S,17R)-17-acetoxy-3-hydroxy-10,13-dimethyl-2-morpholinohe} \text{decahydro-1H-cyclopenta[a]henanthrene-16-yl)-1-allylpyrroldinidium bromide}\]

Mechanism of action:[66]
It shows its action by competitively antagonize nicotinic acetyl-choline receptors at the neuromuscular junction.
Uses: It is used in modern anaesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation[66]

**Teniloxazine**

![Chemical structure of Teniloxazine]

\[\text{2-[[2-(thiophen-2-ylmethyl)-phenoxy]-methyl]-morpholine}\]

Mechanism of action: It shows its action by inhibiting norepinephrine reuptake, with reasonable choosiness over the dopamine transporters and serotonin & also behaves as an antagonist of the 5-HT\textsubscript{2A} receptor.
Uses: It is used as antidepressant drug.[67]

**Tiemonium iodide**

![Chemical structure of Tiemonium iodide]

\[\text{4-[3-hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholin-4-ium iodide}\]
Mechanism of action: It is an antimuscarinic drug. Uses: It is used for the alleviation of muscle spasms of the intestine, biliary system, uterus and urinary bladder in gastrointestinal, biliary, urinary and gynecological diseases.

**Timolol**

\[
\text{(S)-1-(tert-buty lamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]-propan-2-ol}
\]

Mechanism of action:

- It blocks beta-receptor on the ciliary epithelium
- Block endogenous adrenergic stimulation
- Reduction in the formation of liquid (aqueous humor)
- Reduction of the pressure within the eye (intraocular pressure)
- Reduce risk of damage to the optic nerve & loss of vision in Glaucoma patients

Fig 18. Mechanism of action of Timolol

**Uses:** It is indicated for treatment of glaucoma, heart attacks and hypertension.

**Trimetozone**

\[
\text{morpholin-4-yl-(3,4,5-trimethoxyphenyl)-methanone}
\]
Mechanism of action: Not clear
Uses: Used in the treatment of anxiety

**Viloxazine**

![Viloxazine molecule]

(RS)-2-[(2-ethoxyphenoxy)-methyl]-morpholine

Mechanism of action:

**Fig 19. Mechanism of action of Viloxazine**

Uses: It is an antidepressant drug.

**Xamoterol**

![Xamoterol molecule]

(RS)-N-([2-hydroxy-3-(4-hydroxyphenoxy) propyl]amino)-ethyl]morpholine-4-carboxamide

Mechanism of action: It acts by binding to the $\beta_1$ adrenergic receptor.
Uses: It is used as cardiac stimulant.
**Amorolfine**

\[ \text{(±)-(2R,6S)-rel-2,6-Dimethyl-4-[2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]-propyl]-morpholine} \]

Mechanism of action:[76]
It is act by inhibition of ergosterol biosynthesis in the fungal cell membrane.
Uses: It is used for the treatment of *tinea corporis*, *tinea pedis*, onychomycosis & *tinea cruris*.\[77\]

**Pramoxine**

\[ 4[3-(4-Butoxyphenoxy)propyl]morpholine \]

Mechanism of action:[78]
It works by decreasing the permeability of neuronal membranes to sodium ions hence it blocks initiation as well as conduction of nerve impulses.
Uses: It is used to relieves pain and itching.\[79\]

**Finafloxacin**

\[ 8\text{-Cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-hexahydropyrrolo-[3,4-b]-[1,4]oxazin-6(2H)-yl]-4-oxo-1,4-dihydro-3-quinoline-carboxylic acid} \]
Mechanism of action: 

**Finafloxacin**

![Diagram showing Mechanism of action of Finafloxacin]

Uses: It is used for the treatment of a type of ear infection called acute otitis externa. \[81\]

**Fenpropimorph**

\[\text{cis-2,6-Dimethyl-4-}\left(2\text{-methyl-3-}\left[4\text{-}\left(2\text{-methyl-2-propanyl}\right)-\text{phenyl}\right]-\text{propyl}\right)-\text{morpholine or (2R,6S)-4-}\left[3\text{-}\left(4\text{-}\text{tert-butylphenyl}\right)-2\text{-methylpropyl}\right]-2,6\text{-dimethylmorpholine}\]

Mechanism of action: \[82\]

It acts by inhibiting the enzyme fungal Δ^{14} reductases. 

Uses: It is used as fungicide in agriculture. \[82\]

**Phenadoxone**

![Diagram showing Structure of Phenadoxone]

6-Morpholin-4-yl-4,4-diphenylheptan-3-one

Mechanism of action: It is an opioid analgesic drug. \[83\]

Uses: It is withdrawn from the market. \[84\]
**Tridemorph**

![](image)

2,6-Dimethyl-4-tridecylmorpholine

Mechanism of action: [85]
It inhibits sterol biosynthesis in various organism.
Uses: It is used as systemic fungicide. [86]

**Conclusion:**

Like other heterocyclic compounds, morpholine derivatives are also therapeutically active in most of the cases for treatment of various complication of human body. Its extensive therapeutically activity includes anticancer, anti-diabetic, anti-depressant, growth stimulant, anti-emetic, bronchodilator. In this context it is one of the important nuclei which has to be explore more and more. The pathway of research in this nucleus is brighten.

**Declarations**

**Conflict of Interest**

The authors declare no potential conflicts of interest.

**Ethical Approval**

In this study there was no need of human and animal participants.

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